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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/692,439 | 10/22/2003 | David J. Pinsky | 51917-CB-PCT-US/JPW/AJM/A | 8415 |

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John P. White, Esq.
cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

| EXAMINER | |
|---|---|
| SZPERKA, MICHAEL EDWARD | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/692,439 | PINSKY ET AL. | |
| | Examiner | Art Unit | |
| | Michael Szperka | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's response and amendments received may 22, 2007 are acknowledged.

Claims 1-24 and 26-35 have been canceled.

Claims claim 25 has been amended and is under examination in the instant office action.

### *Specification*

2. Applicant's amendments to the specification to update priority information is noted.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claim 25 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn in view of applicant's claim amendments received May 22, 2007.

Specifically applicant has canceled claims 33-35 and has amended independent claim 25 to recite specific Factor IXa compounds that are disclosed in the specification.

5. The rejection of claim 25 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicant's claim amendments received May 22, 2007.

Specifically applicant has canceled claims 33-35 and has amended independent claim 25 to recite specific Factor IXa compounds that are disclosed in the specification.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The rejection of claim 25 under 35 U.S.C. 103(a) as being unpatentable over Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104) in view of Benedict et al. (of record on the 9/20/04 IDS) and in view of King (US Patent 5,589,571) has been obviated by applicant's claim amendments received May 22, 207.

Specifically, applicant has amended claim 25 to recite specific factor IXa compounds. One recited compound is factor IXa chemically inactivated with dansyl-glu-glu-arg-chloromethylketone. Benedict et al. teach the inactivation of factor IXa with glu-glu-arg-chloromethylketone but do not teach dansyl-glu-glu-arg-chloromethylketone, and as such the rejection of record does not account for all limitations of the invention as presently claimed.

### *Double Patenting*

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. The rejection of claim 25 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,316,403 in view of Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104) and in view of King (US Patent 5,589,571) has been withdrawn in view of applicant's claim amendments received May 22, 2007.

Specifically, claims 33-35 have been canceled and independent claim 25 has been amended to recite specific Factor IXa compounds not disclosed by the '403 patent, the '571 patent or Toledo-Pereyra.

10. The following are new grounds of rejection necessitated by applicant's claim amendments received May 22, 2007.

11. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104) in view of Benedict et al. (of record on the 9/20/04 IDS) and in view of the product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem (revision 27 May 1997).

Toledo-Pereyra discloses that at the time the instant invention was made, a skilled artisan knew that "reperfusion injury" was often referred to by the descriptive

physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). Toledo-Pereyra further discloses that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion injury that needs to be treated with pharmacological agents such as heparin to inhibit coagulation (see particularly the right column of page 1099, Table 7, and the right column of page 1103). These teachings differ from the instant claimed invention in that Toledo-Pereyra does not disclose the administration of "Factor IXa compounds" to treat thrombosis in reperfusion injury.

Benedict et al. disclose that inactivated Factor IXa was successfully used to inhibit thrombus formation in vivo (see entire document, particularly the abstract). They further disclose that administration of inactivated factor IXa offers an advantage over the administration of heparin for inhibiting coagulation in that animals treated with heparin suffered from excessive bleeding while animals given inactivated Factor IXa did not manifest excessive bleeding (see particularly figure 4). Benedict et al. disclose making inhibited factor IXa by incubating factor IXa with glu-gly-arg-chloromethyl ketone (see particularly the right column of page 1760).

The product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem teaches that the use of a fluorophore (i.e. dansyl) on the enzyme inhibitor allows for direct monitoring of interactions of the labeled enzyme/inhibitor complex.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer inactivated Factor IXa to patients to treat reperfusion injury. Motivation to do so at the time the invention was made comes from the teachings of Toledo-Pereyra that thrombus formation in reperfusion injury is to be treated with heparin and the teachings of Benedict et al. that inactivated Factor IXa is better than heparin at inhibiting thrombus formation in vivo because unlike heparin, inactivated factor IXa administration does not lead to excessive bleeding. A skilled artisan would be further motivated to substitute dansyl-Glu-Gly-Arg chloromethyl ketone for the Glu-Gly-Arg chloromethyl ketone used by Benedict et al. to inhibit factor IXa because the use of a fluorescently labeled inhibitor allows for the monitoring of the

interactions that take place with the inhibited enzyme as taught by the Calbiochem product use sheet.

12. Claim 25 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,316,403 in view of Toledo-Pereyra (of record) in view of Benedict et al. (of record) and in view of the product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem (revision 27 May 1997).

The claims of the '403 patent recite methods of treating ischemic disorders by administering inactivated factor IX to a patient to inhibit coagulation so as to treat the ischemic disorder in the patient. Dependent claims in the '403 patent recite that factor IX is inactivated at it active site, via chemical inactivation and dansylation (see particularly patented claims 17-19). The claims of the '403 patent differ from the instant claimed invention in that the claims of the '403 patent do not specifically recite reperfusion injury and do not recite that the species of inactivated Factor IX recited in the instant claim.

Toledo-Pereyra discloses that at the time of the instant invention, a skilled artisan would know that "reperfusion injury" is often referred to by the descriptive physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). Toledo-Pereyra further discloses that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion (see particularly the right column of page 1099 and Table 7 on page 1103).

Benedict et al. disclose that factor IXa inactivated with glu-gly-arg-chloromethyl ketone successfully inhibits thrombus formation in vivo (see entire document, particularly the abstract).

The product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem teaches that the use of a fluorophore (i.e. dansyl) on the enzyme inhibitor allows for direct monitoring of interactions of the labeled enzyme/inhibitor complex.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer factor IXa compounds, such as

inactivated factor IX and IXa to treat reperfusion injuries. Motivation to do so comes from the teachings of the '403 patent which teaches that "Factor IXa" compounds are to be administered to inhibit thrombosis in a patient, and the teachings of Toledo-Pereyra that thrombosis is an important pathophysiological even that occurs in reperfusion injury. A person of skill in the art would be motivated to use a factor IXa that has been inhibited with dansyl-Glu-Gly-Arg chloromethyl ketone because Benedict et al. successfully inhibited thrombus formation in vivo using factor IXa inactivated with Glu-Gly-Arg chloromethyl ketone and the Calbiochem product use sheet teaches that use of a labeled inhibitors offers the advantage of being able to detect labeled enzyme/inhibitor complexes.

13. No claims are allowable.

14. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
July 24, 2007

7/30/07
G.R. EWOLDT, PH.D.
PRIMARY EXAMINER